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Review

Tuberculous lymphadenitis in the left axillary misdiagnosed as metastasis: A case report and review of literature

Hui Li [a,b], Qiang Liu [a,*]

[a] *Shandong Medical Imaging Research Institute Affiliated to Shandong University, Jinan, 250021, China*

[b] *Department of Ultrasonic Medicine, Maternal and Children Health Care of Laiwu Municipal Hospital, Laiwu City, 271100, China*

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Abstract

Objective: To understand the imaging demonstrations of the tuberculous (TB) lymphadenitis in axillary and distinguish it from the metastatic lymphadenopathy.

Methods: A 61-year-old Chinese woman images were retrospected after tuberculosis was verified by pathology. And literature about lymphadenopathy in axillary were retrospected.

Results: Most of the lymph nodes (LN) which infected by Mycobacterium were swollen tend to round, hypo echoic, without obvious hilus, rich in blood flow with branch-like distribution. Most of them had clear border. But the lymph which had a collapse could have an illegible border.

Conclusion: The TB LNs could show some performances similar to metastasis such as hypoechoic, tending to round and rich in blood. But there are some differences between TB and metastatic LN. 1) The hypo echoic TB LNs were homogenous with clear border and smooth edge. The metastatic ones usually have unsmooth edge with spicular or process. 2) Some lymph nodes with collapse and strip shaped hyper echoic areas could be detected in TB patient, that could coexistent with hypoechoic round LNs. 3) The distribution of the rich blood flow in the TB nodes was not distorted, but with branch-like shaped and distributed smoothly. It must be considered about some particular infections during the ultrasonic examinations of swelling LNs in axillary, especially there is no significant lump in the breasts.

Keywords: Extrapulmonary tuberculosis; Tuberculous lymphadenitis; Ultrasound; Breast carcinoma

1. Introduction

Both morbidity of TB and breast carcinoma are increasing in recent years, especially in the developing countries. According to the World Health Organization's global tuberculosis report of 2015, about 9.6 million of the world populations were infected by tuberculosis bacterium. There were 1.5 million patients died from TB in 2014 all over the world [1]. Compared with the pulmonary TB (PTB), extrapulmonary TB (EPTB) has a lower incidence rate. EPTB include pelvic tuberculosis, tuberculous lymphadenitis, skin tuberculosis and so on. Tuberculous lymphadenitis took up a proportion of about 2%–5% in all of the TB cases [2]. Which is found in cervix mostly, followed by the mediastinum and the axillary? According to the current reports, tuberculous lymphadenitis is more common in children, women and the immunosuppressed patients, such as HIV patients [3].

2. Materials and methods

A 61-year-old Chinese female, who was immunocompetent and HIV negative was sent to our institution. She didn't have obvious night sweat or low grade fever which could be aware by herself recently. The lumps in her left axillary were found by chance for one month which didn't cause an obvious pain,

* Corresponding author. Shandong Medical Imaging Research Institute, 324# Jing Wu Road, Jinan City, 250021, China.

E-mail address: 2002md@163.com (Q. Liu).

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and which was diagnosed as left breast carcinoma with lymphatic metastasis in another hospital. She was transferred to our hospital for a surgery of breast cancer. An ultrasonic examination of bilateral breasts was performed before surgery and found there was no space occupying lesion in the bilateral breasts, there is only a lipoma in the subcutaneous fat of left breast which was palpable when touched by hands. It was found that the ultrasonic images manifestations of the swollen LNs didn't support the metastases. She was diagnosed as tuberculous lymphadenitis in our institution. Finally, that was verified by the surgical pathology (Fig. 1). We retrospected the ultrasonic images and some relevant literature to get the ultrasonic features of the tuberculous lymphadenitis and distinguish it from the lymphatic metastasis.

3. Results

The ultrasonic images show: There were 5 swollen LNs whose sizes ranged from 0.83 × 0.60 cm to 2.05 × 1.14 cm in her left axillary. The ultrasonic features of the nodes were followed:

3.1. Shape

The LNs with short to long axes (S/L) ratios greater than 0.5 (Fig. 2). One of them tend to be round with S/L ratio of 0.914. Two of them with several collapses which made them irregular in shape (Fig. 3).

3.2. Echogenicity

The LNs were predominantly hypoechoic. Some strip shaped hyperechoic can be found in the 2 irregular ones. The other 3 LNs were homogenously hypoechoic.

3.3. Border

3 of them had clear borders. The LNs which had collapses could have an illegible border because of the strip shaped hyper echoic generated posterior ultrasonic attenuation.

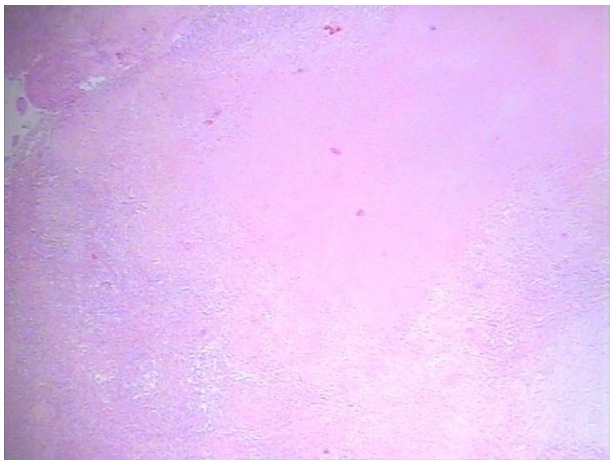

Fig. 1. The figure show the pathological change of one node, there was caseation dyed in red which is the characteristic change of TB.

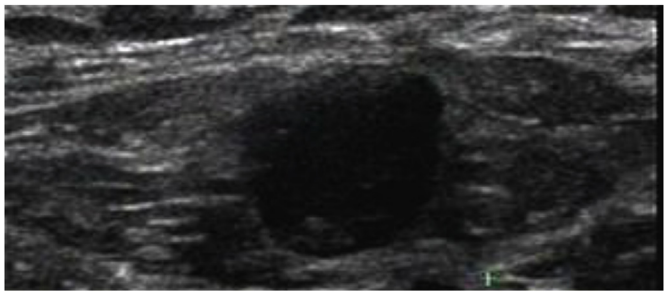

Fig. 2. This is one of the lymph node which tend to be round in shape with well-defined borders and without obvious Hilus.

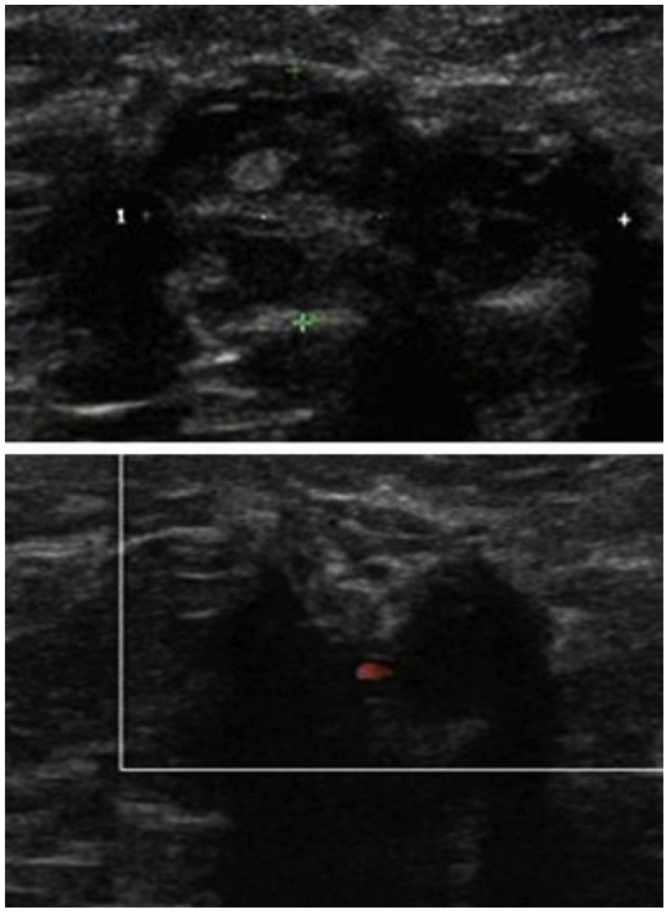

Fig. 3. The two of nodes in the figure show some collapses and with some strip shaped hyperechogenic in them which made some ultrasonic decay.

3.4. Echoic hilus

The echoic hilus appears as a linear hyperechoic structure which is continuous with the adjacent fat in the nodes [4]. The LNs in this case did not show obvious echoic hilus. Only one LN had a very small hyperechoic area at one side of the LN, there was not obvious continuity with the fat surrounding the LN. And it seemed an incomplete hilum.

3.5. Ancillary features

There was not obvious change about the adjacent and matting soft tissue in the ultrasonic images.

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3.6. Vascular distribution

The LNs had rich blood flow, especially the round and hypoechoic ones. 3 of them had branch-like blood flow which could reach the margin of the nodes, with smooth distributions (Fig. 4). In the 2 irregular ones, only some punctiform or striped blood flow signs were detected.

3.7. Vascular resistance

Vascular resistance (RI) ranged from 4.7 to 6.1 in this case.

3.8. Necrosis

There was not any obvious necrosis in this case.

4. Discussion

A case of a 61-year-old woman with axillary lymphadenitis without obvious lump in the both breasts was presented in this report. Tuberculous lymphadenitis was diagnosed by pathology. Axillary lymphadenitis can be found in many diseases, the breast and tuberculous is the most common in the adult female. In the recent years, TB and breast cancer both are increasing in the incidence. TB is the foremost cause of death from a single infectious agent in humans. It is so called that the breast cancer is the first killer for woman in the world. So in this case it should be taken full account for both of them. The both diseases have some similar imaging expressions, even if it is seldom, they could be concomitant [5]. Jeong Won Lee reported a 39-year-old woman who was verified right breast cancer and right tuberculous lymphadenitis by pathological examination [6]. Although there was no lesion in the breasts, considering occult breast carcinoma (OBC), about which obvious space occupying disease can't be found in the breasts by imaging exam, it is a dilemma for this case. Mukhopadhyay reported a 55 years old women who didn't have detectable lesion in either breast was diagnosed right axillary metastatic adenocarcinoma and left axillary tuberculous lymphadenopathy [7]. In addition, OBC even can be found in male [8]. It is usually considered that almost all of those normal or reactive hyperplasia LNs have a triangular, crescent or oval shape [9]. Although hypoechoic LN with shape tending to round used to see as the characteristic of the metastasis, it should not be diagnosed as breast cancer as soon as swollen hypoechoic LNs which tend to be round were found in the axillary. Another disease must be excluded, especially tuberculous. In this case, the shape of the lymph nodes tend to be round, whose S/L ratio greater than 0.5, much of them showed thickened cortex and absent hilus. These expressions should be found mostly in cancers. But there were some features didn't support the metastasis:

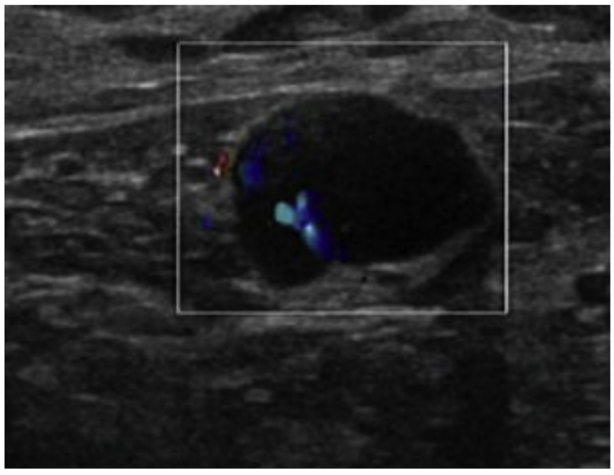

Fig. 4. The node in the figure show rich blood signal from one side to the other with a shape like branch.

1) The distribution of the rich blood flow in the nodes was not distorted, but with branch-like shaped and smoothly distributed.

The rich and smoothly distributed blood flow in the hypoechoic LNs did not support the metastasis. In contrast to it, the blood flow of metastasis is usually tortuous with a high vascular resistance index (RI) [10]. And the RI in this case was lower than the level reported now.

2) There were some lymph nodes showing collapse and strip shaped hyperechoic in this case which can be seen as a characteristic ultrasonic image feature of TB. The collapse and strip shaped hyperechoic may be caused by prior LNs whose intranodal necrosis were absorbed.

Necrosis can be found as a cystic or equal echoic area within the nodes. Cystic necrosis is more common which show as an echo lucent area. Coagulation necrosis appears as an equal area within LNs but is not continuous with the surrounding fat and does not produce acoustic shadowing. Intranodal necrosis could be the characteristic lesion in pathology. Although in ultrasound it can be also detected in metastasis, in those seldom showed collapsing and strip shaped hyper echoic which may be caused by the fibrosis.

3) The hypoechoic LNs were homogenous with clear border and smooth edge. The metastatic ones usually have unsmooth edge, they could have spicular or process. Sometimes the metastasis could have unclear border.
4) There was not obvious edema around the LNs, it reminded that the case was more likely to be a chronic infection.

Many diseases could lead to lymphadenopathy in axillary. The ultrasonic image expressions could have some overlaps among different diseases, even between benign and malignancy. It makes that difficult to give a accurate diagnosis for ultrasound doctors. Even so the ultrasound examination of axillary is important and common method for clinical to classify and confirm stage of diseases [11]. It makes that more necessary to understand the ultrasonic features of axillary LNs. We discuss as follows:

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4.1. Size

The long diameter above 1 cm and short diameter above 0.5 cm used to be the standard for lymph node swollen. As well, nodal size used to be a criterion to distinguish benign from malignant diseases [12]. Actually a normal LN in axillary could be larger than that. Although malignant nodes tend to be larger, reactive lymph nodes can be as large as malignant nodes. In addition, LN with micro-metastases may be small. Some researchers injected tumor cells into the subiliac LNs of mouse to induce metastasis to the proper axillary LNs. They found that proper axillary LN volume which measured by high frequency ultrasound imaging had not increased significantly when metastasis was detected by in vivo bioluminescence [13]. In the case we reported, some LNs less than 1.0 cm in long diameter, but more than 0.5 cm in short diameter were proved infected by TB. So the size of LN is not important feature in ultrasound to determine if the LN is normal or distinguish the cause of the abnormal LN. Now the size is used to assess the stage of disease compared with the former examinations mostly.

4.2. Shape

Shape of the swollen LN is an important information to distinguish the causes of lymphadenopathy. Reactive hyperplasia LN is usually oval. But metastasis tends to be round. The S/L ratio is usually used for describing the shape of LN, and the ratio above 0.5 is supposed to the standard of metastasis [12]. Sung Eun Song reported that the sensitivity of the cortex-hilum (C/H) area ratio was superior to that of the S/L ratio and the specificity were similar [14]. Even so the shape also can't be the sole feature to determine the nature of LN, Moreover some benign diseases also could lead to LN swollen tending to be round [15], such as tuberculosis like the case of this report. The C/H in this report also is high, which indicated by the thickening cortex and absent of hilum. It is also reported that swollen axillary LN in the cat scratch disease could be round and hypoechoic [16]. Despite the shape can give important information to determine if the LN is normal. But we can't know the reason which leads to the abnormality.

4.3. Echogenicity

The echogenicity of swollen LNs could be hypoechoic, anechoic, hyperechoic, which depend on the kind of disease. Fernando Collado-Mesa reported a case of a woman was detected hyperechoic LNs in contralateral axillary because of her breast implant [17]. It is used to be determined that malignancy is usually hypoechoic [15]. And the lymphoma is usually anechoic. Some diseases may lead to variations of echoic in different stages. In this case echo were not completely consistent, maybe because the LNs were infected at different times. The coexistence of LNs which were slightly hyperechoic and hypoechoic could be seen as a characteristic of TB. Therefore the echogenicity also give important information to determine the cause of lymphadenopathy.

4.4. Border

Metastatic axillary LNs usually have sharp borders, whereas benign nodes tend to have unsharp borders [18]. The presence of sharp borders in metastatic nodes is supposed related to infiltrating tumor cells, which replace the normal nodal tissues, causing an increased difference in acoustic impedance between the nodal tissue and surrounding soft tissues. However, unsharp borders also the indication of extranodal spreading. Inflammatory nodes could also cause blurring border between the nodes and surrounding soft tissues. So what determine the border of axillary LNs not only the cause of the disease but also the stage of the diseases. There are some overlaps between the metastasis and infections. So, in the case we reported both kinds of border were detected. Because there were not obvious erosion to the surrounding tissue, the border was clear. But as result of the fibrosis formation which could lead to shadow, the border of some LNs seems unclear. That made difference from the metastasis which have unclear border.

4.5. Echogenic hilum

Loss of the echogenic hilum used to be seen a malignant manifestation in LNs. But it is not specific, some benign disease could also lead to the loss of hilum. Kim SJ research a group of patients without malignancy, loss of hilum observed with a frequency of 79.5% [15]. Loss of echogenic hilum could be found in most of LNs in this case we discussed. Although the hilum lost but the blood flow is still as normal. That maybe a difference from the metastasis. And common infections usually don't have so rich blood flow and not loss of hilum.

4.6. Calcification

Intranodal calcification is generally rare in metastatic axillary LNs. It may be found in irradiated metastatic LNs and lymphomatous nodes after chemotherapy, and often found in tuberculous nodes which existed for a time [19]. So when there were several calcifications in single axillary LN tuberculosis should be thought over. In this case there was not obvious calcification detected. The rough spot and small striped shape hyperechoic could be seen as fibrosis because the echogenity is like the surrounding fibrosis tissue and there was not obvious shadow like stones behind them. If there was some calcification in this case, the diagnosis before surgery would be more sure.

4.7. Internal echogenicity

Benign lymphadenitis usually homogeneous with internal echogenicity. The internal cyst necrosis in the nodes usually detected in the metastasis which performed anechoic areas in the nodes. But cyst also can be found in some suppurative lymphadenitis [20]. Internal cyst could exist in tuberculous lymphadenitis [18,21]. Nagaraju reported a woman whose

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axillary LNs were swollen with cyst areas was verified as Kikuchi-Fujimoto disease [22]. Coagulation necrosis is relatively seldom and appears as an equal echoic area within LNs which is not continuous with the adjacent fat tissue and does not have an posterior shadow. It is taken as the characteristic feature of the TB, regardless of the size of the nodes, the existing of cyst areas or equal echoic areas is helpful to the ultrasound diagnosis. But in this case it is not found in the ultrasonic image, but could be found in the pathological image, maybe because the ultrasonic probe didn't have sufficient high resolution.

4.8. The adjacent echogenicity

Edema of matting and adjacent soft tissue surrounding the swollen axillary LNs are common in infections such as tuberculosis because of the inflammatory reaction [17]. It usually performs hyperechoic with blurring border. However, when metastatic nodes spread invading adjacent soft tissues leading to edema. In addition, post radiation also could lead to matting and adjacent soft tissue edema. In this case there was not obvious change about the adjacent and matting soft tissue in the ultrasonic images, it maybe because the inflammation was not so serious. It maybe could see as a characteristic of the chronic infection.

4.9. Doppler ultrasonography

The pattern of vascular distribution in the LN performs in branch-like type normally. Normal LNs generally show hilar predominant vascularity with a shape of branch. Inflammatory LNs are typically rich in blood signs without changes of the predominant hilar vessel architecture. It is supposed that peripheral type on power Doppler imaging is malignant feature [23]. Sung Eun Song et al. reported that peripheral type on power Doppler imaging obtained sensitivity of 29.4%, specificity of 89.1%, positive predictive value (PPV) of 66.6%, negative predictive value (NPV) 63.0%, it didn't have a enough good sensibility when considered singly [14]. In this case, though the blood flow signs could reach the peripheral area in the node, but it was not the peripheral dominant. And the distribution was smooth with a branch-like type. With spectral Doppler ultrasonography, the vascular resistance (RI) and pulsatility index (PI) of the intranodal vessels can be estimated. Although, the critical value of RI in distinguishing malignant from benign nodes remains controversial. Most of the researches reported that the RI and PI of metastatic LNs are higher than those of reactive ones. Hrazdira I recommended a cut-off of RI as 0.8 and PI as 1.8 [24]. Choi MY researched a group of 43 patients and reported that the mean RI was 0.92 ± 0.23 in LNs involved with metastases and 0.59 ± 0.11 in LNs affected by benign diseases. The mean PI was 2.66 ± 1.59 in LNs involved with metastases and 0.90 ± 0.23 in LNs affected by benign diseases [25]. In this case the RI accorded with the benign diseases of the former researches.

4.10. Elastography

Elastography can generally be classified into qualitative and quantitative assessments. Using qualitative real-time elastic ultrasound, a compression force is applied to the region of interest (ROI) to measure its stiffness. The stiffness of the ROI is estimated by evaluating the degree of local tissue displacements before and after the compression force is applied. In the map of qualitative assessment, stiffness of the LNs is color coded. Elastic image are usually classified into 4 to 5 grades according to the proportion of hard in ROI. Previous studies suggested benign LNs tend to be soft, whereas malignant ones are usually hard [26,27]. But recently, some studies found malignancy could be soft in the elastic image [28], so the method is controversial and is not used popular. For quantitative assessment, the stiffness of the ROI can be quantified by conventional strain elastic image using the strain index or by shear wave elastic imaging (SWE). Quantitative assessment is a recent development in soft tissue elasticity imaging. With the use of ultrafast ultrasound tracking techniques, the speed of the shear wave propagation is measured and the stiffness of the soft tissue is obtained. It is considered that more predictive for elastic nature of the lesions [28]. When research of ex vivo axillary LNs, Kilic F found that cortical thickness had the highest diagnostic performance, followed by cortical stiffness [29]. Park YM et al. also pointed out that Added elastic imaging does not improve the diagnostic ability of conventional ultrasound when evaluating abnormal axillary LNs [30]. Although it still limited, the quantitative assessment can remove some interference factors to get a relative precise stiffness, it maybe give some supplementary information in the diagnosis of the axillary LNs. Because the limited to the instrument, we didn't get the elastic information.

4.11. Contrast-enhanced ultrasonography

Contrast-enhanced ultrasonography allows more accurate evaluation of nodal vascularity and provides information on LN parenchymal perfusion. However, the value of this technique in distinguishing the cause of swollen LNs is controversial. Some researchers reported that it could improve the accuracy in distinguishing benign and malignancy LNs [31,32]. Matsuzawa F reported that the detection of metastasis based on contrast enhanced computed tomography attained sensitivity 20.0%, specificity 88.2%, PPV 60.0%, NPV 55.6%, accuracy 56.3%. Based on color Doppler ultrasonography, the results were sensitivity 36.4%, specificity 95.2%, PPV 80.0%, NPV 74.1%, accuracy 75.0%. Based on contrast enhanced ultrasonography with Sonazoid, the results were sensitivity 81.8%, specificity 95.2%, PPV 90.0%, NPV 90.9%, accuracy 90.6% [33]. Steppan I reported that the malignant LNs increased more vascular signals than the benign ones after Contrast-enhanced ultrasound examination, especially on the peripheral [34]. However, others have reported that it does not increase the accuracy of grey scale and Doppler ultrasonography for identifying malignant LNs. Although contrast

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enhancement may provide additional information about vascularity of axillary lymph nodes which can't be detected by the color Doppler, the value of this technique in routine clinical practice is limited, because the contrast agent needed is expensive, and it needs too much more time if there are several LNs.

4.12. Fine needle aspiration cytology (FNAC)

If we don't get the idea after thinking over all the imaging information, FNAC maybe needed. FNAC could determine the causes of lymphadenopathy in most cases [35]. FNAC is popular by the clinical doctor because it is convenient and could get a pathological diagnosis rapidly. It could help some patients avoiding unnecessary operations by confirming disease rapidly by cytology [36]. It is the key to get the marking cells of diseases. If the suspicious lesions didn't be punctured, some disease could be missed [37]. Ultrasound guided FNAC could ensure to get the correct lesion and get the marking cells more likely [38]. Some factors would influence sensitivity of ultrasound guided FNAC, such as the size, Cortical thickness and so on [39]. Even so ultrasound guided FNAC is safe and time-consuming, that make it more popular in clinical especially for preoperative assessment recently [40,41]. Though the trauma is so limited, we should still improve the knowledge of the B-mode and color Doppler images to give an accurate diagnosis rapidly and without trauma.

In short, there were many causes which could lead to lymphadenopathy in axillary, such as various kinds of infections, metastatic diseases and lymphoma. Moreover, the swollen axillary LNs should be distinguished from other lesions, such as lipoma, schwannoma, hemangioma, fibromatosis, epidermoid cysts, and malignant fibrous histiocytomas and so on [42]. In view of its relatively rare incidence but accurate prognosis due to antituberculous medication, it is important to distinguish tuberculous lymphadenitis from the other causes of lymphadenopathy in adults, especially with or without lump in the breasts, which is the key for the clinician to choose the next medical treatment.

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